Paper No. 15

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte T. TANIGUCHI, JOHN M. ROLF,
PRABIR BHATTACHARYA, and YAHIRO UEMURA

Appeal No. 1996-4119
Application No. 08/261,406

ON BRIEF

Before, SPIEGEL, ADAMS and MILLS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 2, 4, 5, 8-16, 18-20, and 22. We note that no statement is made by the examiner regarding the status of claim 17[1]. In addition, the examiner (Answer[2], page 1) indicated that claim 7 would be allowable if written in independent form.

Claims[3] 1[4] and 5 are illustrative of the subject matter on appeal and are reproduced below:

1. A process for purifying α_1-proteinase inhibitor comprising:
providing an impure protein fraction comprising α_1-proteinase inhibitor;
suspending the impure protein fraction comprising α_1-proteinase inhibitor in water;
precipitating the impure protein fraction comprising α_1-proteinase inhibitor with a precipitant comprising PEG and $ZnCl_2$;
collecting the supernatant from the PEG/ $ZnCl_2$ precipitation, wherein the supernatant comprises α_1-proteinase inhibitor;
precipitating α_1-proteinase inhibitor from the PEG/$ZnCl_2$ supernatant with $ZnCl_2$ to thereby provide an α_1-proteinase inhibitor precipitate;
resuspending the α_1-proteinase inhibitor precipitate in an aqueous medium;
applying the resuspended α_1-proteinase inhibitor to an anion-exchange chromatography medium;

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[1] Claim 17 was also not addressed in the Final Action (Paper No. 6, mailed April 4, 1995). However, appellants view (Brief, page 2, part 3) claim 17 as included in the rejection under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng and Harris. Accordingly, we will include claim 17 with the rejection under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng and Harris.
[2] Paper No. 14, mailed April 16, 1996.
[3] While the Answer makes no mention of it, appellants' Appendix of Claims is replete with typographical errors. In this regard we refer to the original claims, or the claims as amended (Paper No. 5, received December 5, 1994 and Paper No. 8, received September 25, 1995).
[4] Claim 1 is reproduced as it appears in Paper No. 8 (received September 25, 1995).

recovering a fraction comprising α_1 proteinase inhibitor from the anion-exchange chromatography medium;

applying α_1-proteinase inhibitor recovered from the anion-exchange chromatography medium to a metal chelate medium; and

recovering a fraction comprising α_1-proteinase inhibitor from the metal chelate medium.

5. A process as recited in claim 1 wherein the $ZnCl_2$ is added to the impure protein fraction to a concentration of 0.25 to 0.75 mM.

The references relied upon by the examiner are:

Neurath et al. (Neurath)	4,540,573	Sep. 10, 1985
Bollen et al. (Bollen)	4,629,567	Dec. 16, 1986

Protein Purification Methods, a practical approach 154-170 (E. L. V. Harris & S. Angal eds., IRL Press, Oxford 1989) (Harris)

Bischoff et al., "Purification and Biochemical Characterization of Recombinant α_1-Antitrypsin Variants Expressed in Escherichia coli," Vol. 30, pp. 3464-3472 (1991)

Ng et al. (Ng), "Plasma Protein Recovery from Spent Tissue Culture Fluid," Biotechnology Letters, Vol. 13(4), pp. 261-264 (1991)

Yip et al. (Yip), Immobilized Metal Ion Affinity Chromatography, in Methods in Molecular Biology 17-31 (A. Kenney & S. Fowell eds, The Humana Press Inc., 1992)

GROUNDS OF REJECTION[5]

Claims 1, 2, 4, 5, 8, 17[6] and 22[7] are rejected under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng and Harris.

Claims 9-16, 18 and 19 are rejected under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng and Harris as applied to claims[8] 1, 2, 4, 5, 8, 17[9] and 22[10] and further in view of Neurath and Yip.

Claim 20 is rejected under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng, Harris, Neurath and Yip as applied to claims 9-16, 18 and 19, and further in view of Bischoff.

We affirm.

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[5] We note the examiner withdrew (Answer, bridging paragraph, pages 1-2) the rejection of claim 7, under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng and Harris (Final Rejection, Paper No.6, mailed April 4, 1995) indicating that it would be allowable if rewritten in independent form. Claim 7 is now (Answer, page 1) "objected to as being dependent upon a rejected base claim." Accordingly, we will not address claim 7 as it was indicated as allowable.

[6] See supra, n.1.

[7] We note that appellants refer to "[c]laims 1, 2, 4, 5, 7, 8, 17 and 21" in their "STATUS OF CLAIMS" section of the Brief (page 2). However, appellants after final amendment (Paper No. 8, received September 25, 1995) canceled claim 21. The reference to claim "21" should be to claim "22." This typographical error was corrected herein.

[8] We note the following typographical error. The examiner included a reference to claim 7 in this statement of the rejection. However, the examiner withdrew the rejection of claim 7 (see supra, n.5). Therefore, claim 7 should not be included in this statement of rejection. This typographical error was corrected herein.

[9] See supra, n.1.

[10] We note the typographical error in the examiner's statement of the rejection (Answer, page 7), wherein reference is made to claim "21." Claim 21 was canceled by appellants' after final amendment (Paper No. 8, received September 25, 1995). The examiner should have referred to claim "22" and not claim "21". This typographical error was corrected herein.

DISCUSSION

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, and to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's Answer for the examiner's reasoning in support of the rejection. We further reference appellants' Brief[11] for the appellants' arguments in favor of patentability.

CLAIM GROUPING:

Appellants set forth two groupings (Brief, page 5) of claims. Group I: claims 1, 2, 4, 5, 7-20 and 22[12] and Group II: claims 5 and 7[13]. Accordingly, we limit our discussion to claims 1, and 5.

THE REJECTIONS UNDER 35 U.S.C. § 103:

Obviousness is a legal conclusion based on the underlying facts. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966); Continental Can Co. Inc. v. Monsanto Co., 948 F.2d 1264, 1270, 20 USPQ2d 1746, 1750 (Fed. Cir. 1991); Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1566-68, 1 USPQ2d 1593, 1595-97 (Fed. Cir.), cert. denied, 481 U.S. 1052 (1987).

[11] Paper No. 13, received January 29, 1996
[12] We note that appellants refer to "[c]laims 1-22" in their grouping of claims (Brief, page 5). However, claims 3 and 6 were canceled in appellants amendment (Paper No. 5, received December 5, 1994) and claim 21 was canceled in appellants after final amendment (Paper No. 8, received September 25, 1995). The typographical error was corrected herein.
[13] See supra, n.5.

Claim 1:

The examiner states (Answer, bridging paragraph, pages 5-6):

> It would have been obvious to one with ordinary skill in the art at the time [a]ppellants' invention was made to determine all operable and optimal parameters the purification of alpha-1-antitrypsin by Bollens' procedure as modified by Ng and Harris, such as the volume the impure protein is suspended in, in what the protein is suspended, and the concentration of the PEG/$ZnCl_2$ precipitant because it is desirable to choose buffer conditions and to have the components of a precipitation present in ratios that insure the highest yield and purity of the protein that is being purified. Further, it would have been obvious to one with ordinary skill in the art at the time [a]ppellants' invention was made to insert an additional anion-exchange chromatography step after the first anion-exchange step in the purification process of alpha-1-antitrypsin by the protocol of Bollen as modified by Ng and Harris, because it is desirable in the art to purify a therapeutic product to the greatest extent possible in order to produce a product having few impurities, and having homogeneous properties, and additional purification steps would accomplish this.

As noted by the examiner (Answer, page 4) Bollen discloses all the process steps of appellants' claim 1, except the use of $ZnCl_2$ in the PEG precipitation step and a separate $ZnCl_2$ precipitation step. Bollen discloses (column 4, lines 3-21) the use of a Tris-HCl buffer and a phosphate buffer, both of which comprise water. Therefore, Bollen does disclose "suspending the impure protein fraction comprising α_1-proteinase inhibitor in water," as recited in appellants' claim 1. Bollen also discloses the use of ammonium sulfate precipitation (column 2, line 42, to column 3, line 4).

Appellants state (Brief, page 8) that "claim 1 requires the precipitation of unwanted proteins by the addition of PEG and $ZnCl_2$, leaving alpha-1-proteinase

inhibitor in solution, and thereafter precipitating the alpha-1-proteinase inhibitor by the addition of more $ZnCl_2$." Appellants then argue (Brief, page 9) that the examiner does not point to prior art suggesting such a selective precipitation.

Bollen discloses (column 2, lines 48-52) "[a] crude bacterial or yeast extract is preferably partially purified such as by selective ammonium sulfate precipitation followed by … selective precipitation of contaminating proteins such as by use of a polyalkyleneglycol." Reversing the order of process steps is prima facie obvious in the absence of new or unexpected results. In re Burhans, 154 F.2d 690, 692, 69 USPQ 330, 332 (CCPA 1946). We find no evidence of record demonstrating that the claimed process produces an unexpectedly different result than that of the prior art process. Therefore, it would have been prima facie obvious to reverse the steps disclosed in Bollen to first use a polyalkyleneglycol (e.g. PEG), followed by precipitation with a salt (ammonium sulfate).

The examiner applies Ng (Answer, page 4) to teach the use of zinc chloride precipitation to purify proteins. Where, as here, the prior art recognizes two components to be equivalent, an express suggestion to substitute one for another need not be present in order to render such substitution obvious. In re Fout, 675 F.2d, 301, 213 USPQ 532, 536 (CCPA 1982). Therefore, in our opinion, it would have been prima facie obvious to substitute $ZnCl_2$, for the ammonium sulfate taught by Bollen.

The examiner provides Harris to teach that salts (page 154) and PEG (page 160) are routinely used for precipitating proteins. Harris teach (page 160) with

reference to PEG that "[t]he mechanism of precipitation is similar to that of precipitating by organic solvents." In re Mills, 470 F.2d 649, 651, 176 USPQ 196, 198 (CCPA 1972)("[a]ll the disclosures in a reference must be evaluated"). Harris teaches (pages 157-160) precipitation by organic solvents. Harris teaches (page 159) with respect to organic solvents that "[t]he ionic strength of the solution should be between 0.05-0.2." As the mechanism of PEG precipitation is similar to that of organic solvent precipitation, one would expect ionic strength to be relevant in PEG precipitation as well. In this regard, we note that appellants' claim 1 "suspends the impure protein fraction comprising α_1-proteinase inhibitor in water." While Bollen does not make an express statement regarding the addition of salt to the PEG precipitation, we note that Bollen discloses (column 4, lines 3-21) using a Tris-HCl, or phosphate buffer for the PEG precipitation, thus maintaining the appropriate ionic strength for the precipitation. In our opinion, it would have been prima facie obvious to use $ZnCl_2$, to maintain the ionic strength, since $ZnCl_2$, and a metal chelate column (which can be a Zn^{++} chelate column) are used in subsequent purification steps.

Therefore, we are not persuaded by appellants' argument (Brief, page 11) that "[h]ere, there is simply no suggestion in the prior art as a whole to combine the various specific process steps, even if individually they were known to achieve applicants' process." Appellants' rely (Brief, page 10) on the disclosure in Bollen (column 2, lines 7-12) that "… While the individual steps are, in a general sense, standard protein purification techniques, particular steps in a particular sequence must be selected from the myriad possibilities of process steps and sequences to

achieve a purification process which is effective and efficient." However, Bollen also discloses (column 3, lines 49-54) that the "AAT resulting from this procedure can, if desired, be subjected to further purification steps to remove trace contaminants such as by affinity chromatography." Therefore, we are not persuaded by appellants' reference to Bollen (column 2, lines 7-12).

In our opinion, the examiner met her burden of establishing a prima facie case of obviousness.

Claim 5:

Appellants argue (Brief, page 11) that "[t]here is certainly nothing in Figure 1 of Ng, or any other part of that article suggesting the use of 0.25 to 0.75 mM $ZnCl_2$ in combination with PEG to selectively precipitate impurity proteins, but not α_1-proteinase inhibitor."

The examiner applies Ng to teach that $ZnCl_2$, can be used to precipitate proteins. As discussed supra, in our opinion, it would have been prima facie obvious to use $ZnCl_2$, to maintain the ionic strength of the solution, since $ZnCl_2$, and a metal chelate column (which can be a Zn^{++} chelate column) are used in subsequent purification steps.

Harris teaches (page 159) the ionic strength of the solution should be between 0.05-0.2. With regard to the difference between the ionic strength taught by Harris and the "concentration of 0.25 to 0.75" limitation of apellants' claim 5, we note that the discovery of an optimum value of a result effective variable is ordinarily within the skill of the art. In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219

(CCPA 1980). We find no evidence of record that this result effective variable is not within the ordinary skill of the art, or that an unexpected result was obtained.

Therefore, in our opinion, the examiner met her burden of establishing a prima facie case of obviousness.

Accordingly, we affirm the examiner's rejection of claims 1, 2, 4, 5, 8, 17[14] and 22 under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng and Harris.

Appellants do not argue the merits of the rejection of claims 9-16, 18 and 19 under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng and Harris as applied to claims[15] 1, 2, 4, 5, 8, 17[16] and 22[17] and further in view of Neurath and Yip. Appellants also do not argue the merits of the rejection of claim 20 under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng,

Harris, Neurath and Yip as applied to claims 9-16, 18 and 19, and further in view of Bischoff.

Therefore, under these circumstances, having found, supra, the examiner met her burden of establishing a prima facie case of obviousness for the rejection of claims 1, 2, 4, 5, 8, 17[18] and 22 under 35 U.S.C. § 103 as being unpatentable over

[14] See supra, n.1.
[15] See supra, n.8.
[16] See supra, n.1.
[17] See supra, n.10.
[18] See supra, n.1.

Bollen in view of Ng and Harris, we are constrained to reach the conclusion that the examiner met her burden of establishing a prima facie case of obviousness for the rejection of claims 9-16, 18 and 19 under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng and Harris as applied to claims[19] 1, 2, 4, 5, 8, 17[20] and 22[21] and further in view of Neurath and Yip. Similarly, we are also constrained to reach the conclusion that the examiner met her burden of establishing a prima facie case of obviousness for the rejection of claim 20 under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng, Harris, Neurath and Yip as applied to claims 9-16, 18 and 19, and further in view of Bischoff.

Accordingly, we affirm the examiner's rejection of claims 9-16, 18 and 19 under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng and Harris as applied to claims[22] 1, 2, 4, 5, 8, 17[23] and 22[24] and further in view of Neurath and Yip. We also affirm the examiner's rejection of claim 20 under 35 U.S.C. § 103 as being unpatentable over Bollen in view of Ng, Harris, Neurath and Yip as applied to claims 9-16, 18 and 19, and further in view of Bischoff.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

[19] See supra, n.8.
[20] See supra, n.1.
[21] See supra, n.10.
[22] See supra, n.8.
[23] See supra, n.1.
[24] See supra, n.10.

AFFIRMED

Carol A. Spiegel	)
Administrative Patent Judge	)
	)
	)
	) BOARD OF PATENT
Donald E. Adams	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
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